AD-A096 331 ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/G 6/20
TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
MAR 81 M J TOPPER, M H WEEKS
UNCLASSIFIED USAEHA-75-51-0156-81 NL

END
DATE FILMED
4-81
DTIC

AEHA

(12) 7w

LEVEL II

UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010

(14) USAEHA-75-51-0156-81, USAEHA-75-51-0158-81.

(6)

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS
AI3-37543 and AI3-37546
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
~~STUDY NOS. 75-51-0156-81 AND 75-51-0158-81~~
SEPTEMBER 1978 - DECEMBER 1980.

Michael L. Topper
Maurice H. Weeks

(9) Final Rpt. Sep 78 - Dec 80

Approved for public release; distribution unlimited.

(11) Mar 81 (12) 17

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER 75-51-0156-81 and 75-51-0158-81	2. GOVT ACCESSION NO. AD-A096331	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Topical Hazard Evaluation Program of Candidate Insect Repellents AI3-37543 and AI3-37546, US Department of Agriculture Proprietary Chemicals, Study Nos. 75-51-0156-81 and 75-51-0158-81, September 1978 - December 1980		5. TYPE OF REPORT & PERIOD COVERED Final, Sep 78 - Dec 80
		6. PERFORMING ORG. REPORT NUMBER 75-51-156, 0158-81
7. AUTHOR(s) MICHAEL J. TOPPER, CPT, VC MAURICE H. WEEKS		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS US Army Environmental Hygiene Agency Aberdeen Proving Ground, MD 21010		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS Commander US Army Health Services Command Fort Sam Houston, TX 78234		12. REPORT DATE Sep 78 - Dec 80
		13. NUMBER OF PAGES 14
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

USDA Proprietary Chemicals	Eye irritation
AI3-37543	Skin irritation
AI3-37546	Photochemical irritation
Topical Hazard Evaluation	ALD
Candidate repellent	Guinea pig sensitization

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Preliminary hazard evaluation of AI3-37543 and AI3-37546 were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemicals did not cause skin, eye, or photo irritation. They did not prove to be acutely toxic by ingestion. It was recommended that both chemicals be approved for further testing as candidate insect repellents.

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

CPT Topper/cf/AUTOVON
584-3980

REPLY TO ATTENTION OF

HSE-LT-T/WP

9 MAR 1981

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents AI3-37543 and AI3-37546, US Department of Agriculture Proprietary Chemicals, Study Nos. 75-51-0156-81 and 75-51-0158-81, September 1978 - December 1980

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

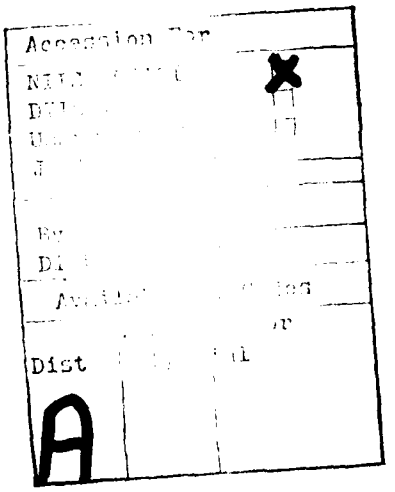
Preliminary hazard evaluations of AI3-37543 and AI3-37546 were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemicals did not cause skin, eye, or photo irritation. They did not prove to be skin sensitizers or to be acutely toxic by ingestion. It was recommended that both chemicals be approved for further testing as candidate insect repellents.

FOR THE COMMANDER:

JOHN F. MAZUR
MAJ, MSC
Director, Laboratory Services

1 Incl
as (5 cy)

CF:
HQDA (DASG-PSP)
Cdr, HSC (HSPA-P)
Dir, Advisory Cen on Tox, NRC
Comdt, AHS (HSA-IPM)
USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Region



DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO ATTENTION OF

HSE-LT-T/WP

TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENTS AI3-37543 and AI3-37546 US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS STUDY NOS. 75-51-0156-81 AND 75-51-0158-81 SEPTEMBER 1978 - DECEMBER 1980

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, Florida, 27 September 1978.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration, titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-37543 and AI3-37546.

4. SUMMARY OF FINDINGS. Hazard evaluation of the candidate repellents AI3-37543 and AI3-37546 were conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:*†

---

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1978.

† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

Study Nos. 75-51-0156-81 and 75-51-0158-81, Sep 78 - Dec 80

TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
SKIN IRRITATION STUDIES		
Rabbits		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits. 0.5 mL technical grade chemical applied to each of six rabbits.	Chemicals AI3-37543 and AI3-37546 did not cause irritation of the intact skin or of the skin surrounding an abrasion. (See Appendices B and C for details.)	USAEHA Category I (ref Appendix A)
EYE IRRITATION STUDIES		
Rabbits		
Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of six New Zealand White rabbits.	Chemicals AI3-37543 and AI3-37546 did not cause irritation to the eyes of rabbits. (See Appendices D and E for details.)	USAEHA Category A (ref Appendix A)
APPROXIMATE LETHAL DOSE (ALD)		
Oral		
Rats (male)-no diluent	AI3-37543 ALD < 1270 mg/kg AI3-37546 ALD = 1270 mg/kg	Neither chemical presents a lethal hazard from accidental ingestion.

Study Nos. 75-51-0156-81 and 75-51-0158-81, Sep 78 - Dec 80

Test	Results	Interpretation
PHOTOCHEMICAL SKIN IRRITATION STUDIES		
Rabbits		
A single 0.05 mL application of a 25-percent (w/v) solution of each chemical and a 10 percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.	A 25-percent solution of AI3-37543 and AI3-37546 in ethanol did not cause photochemical irritation reaction under tests conditions. (See Appendices F and G.)	Chemicals AI3-37543 and AI3-37546 did not cause a photochemical irritation reaction under test conditions and are not expected to cause a photochemical irritation in humans.
Control		
Following UV exposures of the rabbits, 0.05 mL of test chemical, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.	

Study Nos. 75-51-0156-81 and 75-51-0158-81, Sep 78 - Dec 80

Test	Results	Interpretation
SENSITIZATION STUDIES		
Guinea Pigs (Male)		
Intradermal injections of 0.1 mL of a 0.1 percent solution (w/v) of AI3-37543 and AI3-37546 or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		
Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After 2 weeks' rest, they were challenged with ID injections of each test chemical.	Challenge doses of AI3-37543 and AI3-37546 did not produce a sensitization reaction. (See Appendices H and I.)	Chemicals AI3-37543 and AI3-37546 did not produce sensitization reactions under test conditions and are not expected to produce sensitization reactions in man.
Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks' rest, they were challenged with ID injections of DNCB.	Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.	DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.

* A known skin sensitizer

Study Nos. 75-51-0156-81 and 75-51-0158-81, Sep 78 - Dec 80

5. CONCLUSION. Technical grade chemicals AI3-37543 and AI3-37546 did not cause any skin, eye, or photo irritation, no sensitization reaction, and did not prove to be an acute ingestion hazard.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37543 and AI3-37546 be approved for further testing as candidate insect repellents.

MICHAEL J. TOPPER, DVM
CPT, VC
General Veterinary Officer
Toxicology Division

MAURICE H. WEEKS
Chief, Toxicity Evaluation Branch
Toxicology Division

APPROVED:

ARTHUR H. McCREESH, Ph.D.
Chief, Toxicology Division

APPENDIX A

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

COMPOUND: AI3-37543, USDA Proprietary Chemical — AEHA STUDY NO. 75-51-0156-81

PRIMARY SKIN EFFECTS
NEW ZEALAND WHITE RABBITS

USAEHA TOXICITY CATEGORY
I

CONDITIONS -
0.5 mL applied to back of rabbits on 3 abraded and 3 intact skin sites. Covered with 2x2 gauze for 24 hours.

	Time of Observation (Hours)	Response Rabbit No. 961	962	963	964	965	966	Score	Comments
Erythema & Eschar									
Intact Skin	24	0		1		0		1	
Intact Skin	72	0		0		0		0	
Abraded Skin	24		0		0		0	0	
Abraded Skin	72		0		0		0	0	
					Subtotal				
Edema Formulation									
Intact Skin	24	0		0		0		0	
Intact Skin	72	0		0		0		0	
Abraded Skin	24		0		0		0	0	
Abraded Skin	72		0		0		0	0	
					Subtotal			0	
					Total			1	
					Mean			0.17	

APPENDIX C

COMPOUND: AI3-37546, USDA Proprietary Chemical

USAEHA STUDY NO. 75-51-0158-81

PRIMARY SKIN EFFECTS
NEW ZEALAND WHITE RABBITS

USAEHA TOXICITY CATEGORY
I

CONDITIONS -
0.5 mL applied to back of rabbits abraded and 3 intact skin sites. Covered with 2x2 gauze for 24 hours.

	Time of Observation (Hours)	Response Rabbit No. 961	962	963	964	965	966	Mean Score	Comments
Erythema & Eschar									
Intact Skin	24	1		0		0		0.17	
Intact Skin	48	0		0		0		0	
Abraded Skin	24		0		0		0	0	
Abraded Skin	48		0		0		0	0	
					Subtotal				
Edema Formulation									
Intact Skin	24	0		0		0		0	
Intact Skin	48	0		0		0		0	
Abraded Skin	24		0		0		0	0	
Abraded Skin	48		0		0		0	0	
					Subtotal			0	
					Total			0.17	

APPENDIX D

COMPOUND: AI3-37543, USDA Proprietary Chemical — USAEHA STUDY NO. 75-51-0156-81

ACUTE EYE EFFECTS
NEW ZEALAND WHITE RABBITS

USAEHA TOXICITY CATEGORY
A

CONDITIONS -
0.1 mL applied to right eye of six rabbits. Left eye served as the control.

Time of Reading Hrs-Days	Structure	Scores Rabbit No. 761	762	763	764	765	766	Mean Score	Comments
24	cornea	0	15	0	0	0	0	2.5	
	iris	0	0	0	0	0	0	0	
	conjunctivae	0	6	0	0	0	0	1	
48	cornea	0	10	0	0	0	0	1.7	
	iris	0	0	0	0	0	0	0	
	conjunctivae	0	4	0	0	0	0	0.7	
72	cornea	0	0	0	0	0	0	0	
	iris	0	0	0	0	0	0	0	
	conjunctivae	0	0	0	0	0	0	0	
7-days	cornea	0	0	0	0	0	0	0	
	iris	0	0	0	0	0	0	0	
	conjunctivae	0	0	0	0	0	0	0	

APPENDIX E

COMPOUND: AI3-37546, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0158-81
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS	USAEHA TOXICITY CATEGORY A	CONDITIONS - 0.1 mL applied to right eye of six rabbits. Left eye served as the control.

Time of Reading Hrs-Days	Structure	Scores Rabbit No. 803	804	805	806	807	808	Mean Score	Comments
24	Cornea	0	0	0	5	0	0	.83	
	Iris	0	0	0	0	0	0	0	
	Conjunctivae	0	0	2	2	0	0	.66	
48	Cornea	0	0	0	0	0	0	0	
	Iris	0	0	0	0	0	0	0	
	Conjunctivae	0	0	0	0	0	0	0	
72	Cornea	0	0	0	0	0	0	0	
	Iris	0	0	0	0	0	0	0	
	Conjunctivae	0	0	0	0	0	0	0	
7-Days	Cornea	0	0	0	0	0	0	0	..
	Iris	0	0	0	0	0	0	0	
	Conjunctivae	0	0	0	0	0	0	0	

APPENDIX F

PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

COMPOUND: AI3-37543, USDA Proprietary Chemical	USAEHA STUDY NO. 75-51-0156-81
COMMENTS:	
PROCEDURE: 0.05 mL of a 25% (w/v) solution in 95% ethanol was applied to the backs of six rabbits and 0.05 mL of a 10% solution of Oil of Bergamot was used as the control.	

	MEAN SKIN IRRITATION SCORE							
	Test Compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure		Positive Control Non-UV Exposure	
Observation Time	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	4	1	0	0	12	6	9	4
48 Hours	3	1	0	0	9	5	0	0
72 Hours	0	0	0	0	8	4	0	0
TOTAL	7	2	0	0	29	15	9	4
Mean Irritant Responses	0.39	0.11	0	0	1.61	0.83	0.50	0.22
Net Score								

AEHA Form 62, 1 Feb 81 (HSE-LT)

APPENDIX G

PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

COMPOUND: AI3-37546, USDA Proprietary Chemical	USAEHA STUDY NO. 75-51-0158-81
COMMENTS:	
PROCEDURE: 0.05 mL of a 25% (w/v) solution in 95% ethanol was applied to the backs of six rabbits and 0.05 mL of Oil of Bergamot was used as the control.	

	MEAN SKIN IRRITATION SCORE							
	Test Compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure		Positive Control Non-UV Exposure	
Observation Time	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	10	2	7	0	18	16	10	1
48 Hours	5	1	3	1	15	14	8	3
72 Hours	3	1	1	0	12	11	4	2
TOTAL	18	4	11	1	45	41	22	6
Mean Irritant Responses	1.0	0.22	0.6	0.06	2.5	2.28	1.22	0.33
Net Score								

AEHA Form 62, 1 Feb 81 (HSE-11)

COMPOUND: AI3-37543, USDA Proprietary Chemical — STUDY No. 75-51-0156-81

GUINEA PIG SENSITIZATION
MALE
HARTLEY STRAIN

Substance: AI3-37543

Identify:

Positive Control: Dinitzochlorobenzene

Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores				Comments
			Diluent		Test Compound		
	Initial	Final	Initial	Final	Initial	Final	
Test Compound	466	682	0	0	0	2.7	
Positive Control	491	736	0	0	19	356	
Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores				
			Diluent		Test Compound		
	Initial	Final	Initial	Final	Initial	Final	
Test Compound	-	-	0	0	0	0.9	
Positive Control	-	-	0	0	5.4	284	

Final Scores
>100 - Strong Sensitizing
25-100 - Mild Sensitizing
<25 - No Sensitizing

APPENDIX I

COMPOUND: AI3-37546, USDA Proprietary Chemical STUDY NO. 75-51-0158-81

GUINEA PIG SENSITIZATION
MALE
HARTLEY STRAIN

Substance: AI3-37546

Identify:

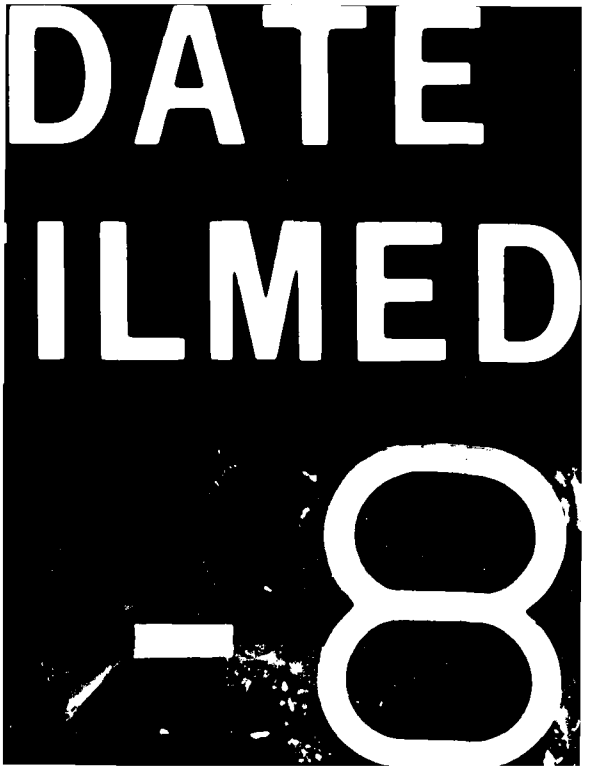
Positive Control: Dinitiochlorobenzene

Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores				Comments
			Diluent		Test Compound		
	Initial	Final	Initial	Final	Initial	Final	
Test Compound	588	801	1.8	0	32	24	
Positive Control	491	736	0	0	19	356	

Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores				
			Diluent		Test Compound		
	Initial	Final	Initial	Final	Initial	Final	
Test Compound	-	-	0.8	0	17.7	19.1	
Positive Control	-	-	0	0	5.4	284	

Final Scores
>100 - Strong Sensitizing
25-100 - Mild Sensitizing
<25 - No Sensitizing

USAEHA FORM 26-4, 9 JUL 79 (HSE-LT)


DATE
ILMED
-8